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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,854	ZANNIS ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,33,34,36,43,44,47,51,53-62 and 64-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,33,34,36,43,44,47,51,53-55, 57,59,61-62, 64-66 and 68-72* is/are rejected.

7)☒ Claim(s) *56,58,60 and 67* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 2/27/06 was entered.

Claims 30, 33-34, 36, 43-44, 47, 51, 53-62, 64-72 are pending in the present application, and they are examined on the merits herein, with SEQ ID NO: 15 (apoE3) and adenoviral vector as the previously elected species. It is noted that SEQ ID NO: 2 is the mature apoE3 amino acid sequence, while SEQ ID NO: 15 is the apoE3 preproprotein containing its N-terminal signal peptide.

Claim Objections

Claim 33 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the method in claim 30 from which claim 33 is dependent upon already recites "a replication-defective adenoviral vector".

Claims 54-55, 57, 59 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because it is not possible that a polypeptide consists of between 185 and 215 amino acids, 203 amino acids, 220 amino acids or 247 amino acids, respectively has at least 90%

sequence identity to SEQ ID NO: 2 containing 299 amino acids, from which all of these claims are dependent on.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 33-34, 36, 43-44, 47, 53-55, 57, 59, 61-62 and 72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new ground of rejection.**

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor without inducing hypertriglyceridemia, said method comprising intravascularly administering to said

mammal a replication-defective adenoviral vector comprising a nucleic acid encoding any secreted polypeptide having at least 90% sequence identity to SEQ ID NO:2, as long as said nucleic acid does not encode amino acids 260-299 of SEQ ID NO:2. Please note that the claims encompass the utilization of an encoded polypeptide containing a carboxyl-terminal region of a mature, native, human apoE as long as the encoded polypeptide does not contain the sequence having amino acids 260-299 of SEQ ID NO: 2.

Apart from the disclosure of amino acid sequences of various human apoE isoforms such as apoE4, apoE3, apoE2, apoE1, apoE2* and apoE2** with SEQ ID NOS: 14-19, respectively, and that the amino-terminal 1-185 residues of human apoE4 are sufficient for binding to lipoprotein remnants to an extent that promotes their efficient clearance in apoE-deficient mice, whereas the carboxyl-terminal 260-299 region of the human apoE4 contributes to hypertriglyceridemia, the specification fails to describe the essential characteristics or elements possessed by a representative number of species for a broad genus of the nucleic acid to be utilized in the method as claimed to lower the total serum cholesterol level without inducing hypertriglyceridemia. For example, the instant specification fails to describe which amino acids to be substituted, deleted or inserted, at which positions and in which combinations, particularly at a carboxyl-terminal region of a mature, native, human apoE, such that an encoded polypeptide having at least 90% sequence identity to SEQ ID NO: 2 but without the amino acid sequence of amino acids 260-299 of SEQ ID NO: 2, still possesses the desired

property, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia.

At the effective filing date (4/6/2000) of the present application, there were few findings indicated that under certain experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE resulted in a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia (Tsukamoto et al., J. Clin. Invest. 100:107-114, 1997; Kashyap et al., J. Clin. Invest. 96:1612-1620, 1995). **More importantly, even one year after the effective filing date of the present application, Applicants still state "The identification of amino acid residues within the carboxyl terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research**" (Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001; page 19785, col. 2, bottom of the first full paragraph). Furthermore, variable isoform-specific effects of apoE polypeptides *in vivo* have also been reported (Yoshida et al., Circulation 104:2820-2825, 2001).

Thus, the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48

USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a representative number of species for a broad genus of a nucleic acid encoding a secreted polypeptide having at least 90% sequence identity to SEQ ID NO:2, wherein said nucleic acid does not encode amino acids 260-290 of SEQ ID NO:2, to be utilized in the method as claimed to lower the total serum cholesterol level without inducing hypertriglyceridemia, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 30, 33-34, 36, 43-44, 47, 53-55, 57,59, 61-62 and 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor, said method comprises intravascularly administering to said mammal a replication defective adenoviral vector encoding a secreted polypeptide consists of residues 1-185, 1-202, 1-229 or 1-259 of any one of SEQ ID Nos. 14-19, with SEQ ID NO: 15 as the elected species, when expressed and secreted

in said mammal, lowers the total serum cholesterol without inducing hypertriglyceridemia,

does not reasonably provide enablement for a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor without inducing hypertriglyceridemia by intravascularly administering to said mammal other recombinant replication-defective adenoviral vector as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. ***This is a modified rejection with a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing the construction of recombinant adenoviruses expressing secreted apoE4 and various secreted truncated forms of apoE4 (e.g., apoE4-185, apoE4-202, apoE4-229, EpoE4-259). In an apoE-deficient mouse model, the recombinant adenoviruses were injected intravenously through the tail vein and the effects of full-length apoE4 and its various truncated forms on cholesterol and triglyceride homeostasis were evaluated. Applicants showed that an

insignificant reduction of the mouse cholesterol level and a severely induced hypertriglyceridemia were observed in apoE-deficient mice treated with full-length apoE4-adenovirus, whereas reduced levels of cholesterol without the induction of hypertriglyceridemia were obtained in animals treated with recombinant adenoviruses expressing the aforementioned truncated forms of apoE4. Applicants further demonstrated that overexpression of either full-length apoE3 or apoE4 is sufficient to induce combined hyperlipedimia (high cholesterol and triglyceride levels) in normal C57BL6 mice, whereas an overexpression of apoE4-202 has no detectable effect on triglyceride levels of the C57BL6 mice.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(a) The breadth of the claims

The claims encompass a method of lowering cholesterol in a mammal expressing a functional low density lipoprotein (LDL) receptor without inducing hypertriglyceridemia, said method comprising intravascularly administering to said mammal a replication-defective adenoviral vector comprising a nucleic acid encoding any secreted polypeptide having at least 90% sequence identity to SEQ ID NO:2, as long as said nucleic acid does not encode amino acids 260-299 of SEQ ID NO:2. The claims encompass the utilization of an encoded polypeptide containing a carboxyl-terminal region of a mature, native, human apoE as long as the encoded polypeptide does not contain the sequence having amino acids 260-299 of SEQ ID NO: 2.

(b) The state and the unpredictability of the art

The nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the present application (4/6/2000), the state of the gene therapy art was and still remains unpredictable with respect to the attainment of desired therapeutic effects, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor, as evidenced by the reviews of Verma et al. (Nature 389:239-242, 1997; IDS), Dang et al. (Clin. Cancer Res. 5:471-474, 1999), Romano et al. (Stem Cells 18:19-39, 2000) and Kawashiri et al. (Curr. Control Trials Cardiovasc. Med. 1:120-127, 2000). Dang et al. stated "Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (page 474, col. 2, last paragraph). Romano et al. stated "The potential therapeutic applications of gene transfer technology are enormous. However, the effectiveness of gene therapy programs is still questioned" (see abstract), and "Despite the latest progress reported in the area of vector design, research strategies still have to tackle critically important issues, such as further improvement of gene transfer technology, especially for *in vivo* gene delivery applications, regulation and control of the transgene expression post-cell transduction, and a variety of complex safety matters. These three main issues are to some extent intertwined and pose severe limitations on the applications of gene transfer technology in therapy" (page 21, col. 1, first paragraph). In

October 2000, Kawashiri et al. still stated "Somatic gene therapy is a viable approach to the therapy of several lipid disorders for which therapies are currently inadequate" and "The next decade is therefore likely to witness several clinical trials of gene therapy for lipid disorders" (see Conclusion section, page 125). Kypreos et al. (FASEB J. 15:1598-1600, 2001) also stated "One major parameter in successful gene therapy approaches is **gene dosage** and **expression levels**....The inability of the truncated apoE forms that lack all or part of the carboxyl-terminal 260-299 region to induce hypertriglyceridemia, coupled with their intact ability to clear cholesterol, makes them attractive candidates in future gene therapy applications to correct remnant removal disorders" (page 1600, col. 2, last paragraph). Thus, it is clear that at the effective filing date of the present application gene therapy for the treatment of any lipid disorder was still immature and not routine.

Additionally, at the effective filing date of the present application (4/6/2000) although substantial evidence in the prior art as well as the findings of the present invention suggested or indicated that ApoE functioned **to decrease cholesterol while increasing triglyceride levels** (see references cited on page 6, lines 4-25 of the instant specification), the findings of Tsukamoto et al. (J. Clin. Invest. 100:107-114, 1997; Cited previously) and Kashyap et al. (J. Clin. Invest. 96:1612-1620, 1995) indicated that under their experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE (299 amino acid residues) resulted in **a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia**. Thus, at the effective filing date of the present

application it was apparent that the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo*, at least in ApoE-deficient mice, was still unpredictable, let alone in any mammal expressing a functional LDL receptor.

The unpredictability of the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo* is further supported by the results of Yoshida et al. (Circulation 104:2820-2825, 2001) that showed that ApoE-deficient mice receiving apoE-/- bone marrow cells that express human apoE3 or apoE2 or apoEcys142 have cholesterol levels increasing with age and the cholesterol levels are not affected by apoE expression (see abstract). Interestingly, the lesion in male apoE3 mice was 40% smaller than that of control mice, while the lesion of apoE2 mice was similar to that of control mice and apoEcys142 mice showed an unexpected and significant increase in lesion size. It is further noted that ApoE2 differs from apoE3 by having a cysteine instead of an arginine at residue 158; and apoEcys142 contains 2 amino acid substitutions: an arginine substitution for cysteine at residue 142 and an arginine for cysteine substitution at residue 112.

(c) The amount of direction or guidance presented

Apart from the exemplification using an apoE-deficient mouse model with recombinant adenoviruses expressing secreted apoE4 or one of the secreted truncated apoE variants apoE4-185, apoE4-202, apoE4-229, EpoE4-259, the instant specification fails to provide sufficient guidance for a skilled artisan on how to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal using a replication-defective adenoviral vector comprising a nucleic acid encoding a secreted polypeptide

as broadly claimed. The instant specification fails to provide sufficient guidance for a skilled artisan on which modification(s), for example deletion, insertion or substitution, in which combination(s), and at which amino acid residues in the encoded secreted polypeptide, particularly in the carboxyl-terminal region of a mature, native, human apoE, as long as said polypeptide having at least 90% sequence identity to SEQ ID NO:2 and does not contain amino acids 260-299 of SEQ ID NO:2, so that the modified polypeptide still possesses the desired properties (lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor). As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. Guo et al. (PNAS 101:9205-9210, 2004) estimated that only about a third of single amino acid changes would completely inactivate the average protein and increasing the number of substitutions additively increases the probability that the protein would be inactivated and that specific proteins may be more or less tolerant to changes (see the entire article). Moreover, even one year after the effective filing date of the present application, Applicants still state "**The identification of amino acid residues within the carboxyl terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research**" (Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001; page 19785, col. 2, bottom of the first full paragraph). Furthermore, Yoshida et al. (Circulation 104:2820-2825, 2001) demonstrated that a single amino acid substitution between ApoE2 and ApoE3 proteins

can have a significant effect in their biological acitivity *in vivo*, let alone for the breadth of the encoded secreted polypeptide to be utilized in the method as claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the gene therapy as well as the relevant art on the biological activity of apoE protein in lowering the total serum cholesterol level without inducing hypertriglyceridemia, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Amendment

The Declaration under 37 CFR 1.132 filed on 2/27/06 is sufficient to overcome the rejection of claims 30,33-34, 36,43-44, 47, 53-55, 57,59, 61-62 and 72 based upon insufficiency of disclosure under 35 USC 112, first paragraph, on the issue of the breadth of the treated mammal in the claimed method.

However, the Declaration is not commensurate with the scope of the instant claims and therefore it is not sufficient to overcome the above rejection based on a new ground of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51, 64-66 and 68-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claim 51 recites the limitation "said polypeptide region" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any polypeptide region in claim 30 from which claim51 is dependent on.

Similarly, claims 64-66 and 68-71 recite the limitation "said region" in line 1 of the claims. There is insufficient antecedent basis for this limitation in the claims. There is no recitation of any region in claim 30 from which claims 64-66 and 68-71 are dependent on.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 30, 33-34, 43-44 and 47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37, 39-40, 42-58 of copending Application No. 11/220,485. ***This is a new ground of rejection.***

The claims of the present application differ from the claims of the copending Application No. 11/220,485 in reciting intravascular administering to a mammal expressing a functional low density LDL receptor a replication-defective adenoviral vector comprising a nucleic acid encoding a secreted polypeptide having at least 90% sequence identity to SEQ ID NO:2, wherein said nucleic acid does not encode amino acids 260-299 of SEQ ID NO:2. The claims of the present application can not be considered to be patentably distinct over claims 37, 39-40, 42-58 of copending Application No. 11/220,485 when there is a specific disclosed embodiment of the co-

pending Application that teaches specifically replication-defective adenovirus mediated transfer of a therapeutic apoE protein comprising a naturally-occurring apoE protein having at least one amino acid substitution in the carboxy-terminal region, including apoE3 with SEQ ID NO:2, into apoE$^{-/-}$ mice by intravenous injection for delivery to a liver (see examples and Summary of the Invention). Accordingly, the claims of the copending Application fall within the scope of claims 30, 33-34, 43-44 and 47 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the method of the copending Application by at least intravascular administering to a mammal expressing a functional LDL receptor (e.g., apoE$^{-/-}$ mice) a replication-defective adenoviral vector expressing a therapeutic apoE protein comprising a naturally-occurring apoE protein having at least one amino acid substitution in the carboxy-terminal region, including apoE3 with SEQ ID NO:2, that support the instant claims. An ordinary skilled artisan would have been motivated to do this because this embodiment is explicitly taught in copending Application as a preferred embodiment as shown by exemplification.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claims are allowed.

Claims 56, 58, 60 and 67 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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